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PD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/997,464	12/23/97	STERN	D 54202/JPW/SB

EXAMINER

HM12/0103

ART UNIT	PAPER NUMBER
1617	9

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DATE MAILED: 01/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

Office Action Summary	Application No. 08/997,464	Applicant(s) Stern et al.
	Examiner Janet M. Kerr	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Oct 18, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-5, 11, and 12* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 11, and 12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicants' amendment, filed on 10/18/99, has been entered.

Claims 6-10 and 13-33 have been canceled.

Claims 1-5, 11 and 12 remain pending.

The amendment filed 10/18/99 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment of "a tumor cell" to a "neuronal tumor cell" is new matter as there is no citation of a neuronal tumor cell in the specification or in the claims as originally filed. Moreover, applicants have not indicated where the specification supports "a neuronal tumor cell" in applicants' Response (see page 6 of applicants' Response).

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite for the following reasons: it is unclear which cell types are suitable for evaluating neurotoxicity; and it is unclear if the cells endogenously express a receptor for advanced glycation end product protein (RAGE) and a mutant presenilin-2 protein or if the cells require transient or stable transfection with vector(s) comprising cDNAs encoding RAGE and/or a mutant presenilin-2. In addition, the phrase "is capable of" renders the claim vague and

indefinite as it is unclear if certain cell culture conditions are required such that the mutant presenilin-2 protein actually causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells. It is suggested that applicants amend the phrase "wherein the mutant presenilin-2 protein is capable of causing increased basal apoptosis" to "wherein the mutant presenilin-2 protein causes increased basal apoptosis".

Claim 4 is rendered vague and indefinite by the phrase "a solid support" as there is no definition or examples of solid supports in the specification. Thus, it is unclear what is encompassed by "a solid support".

Claim 11 is rendered vague and indefinite by the phrase "a compound capable of inhibiting neurotoxicity" as it is unclear if certain conditions are required such that the compound actually inhibits neurotoxicity. It is suggested that applicants amend the phrase "a compound capable of inhibiting neurotoxicity" to "a compound which inhibits neurotoxicity".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for evaluating the ability of a compound to inhibit neurotoxicity comprising contacting a neuronal cell or a neuronally differentiated PC12 cell with a compound, and a pharmaceutical composition for use, *in vitro*, comprising a compound identified by the method, does not reasonably provide enablement for a method for evaluating the ability of a compound to inhibit neurotoxicity comprising contacting any non-neuronal cell with a compound, a compound which is a peptidomimetic, a compound which is bound to a solid support, or a pharmaceutical composition for use, *in vivo*. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a method for evaluating the ability of a compound to inhibit neurotoxicity. In claim 1, the method requires "a cell" which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein. In claim 2, the cell can be a neuronal cell, a glial cell, a microglial cell, an astrocyte, an endothelial cell, a mononuclear cell, a neuronal tumor cell, or a PC12 cell. In claim 4, the compound is bound to a solid support. Claims 11 and 12 are directed to a pharmaceutical composition comprising the compound identified in claim 1.

The specification defines neurotoxicity as encompassing "the negative metabolic, biochemical and physiological effects on a neuronal cell which may result in a debilitation of the neuronal cellular functions, including but not limited to neuronal cell death." In addition, the specification states that "Neurotoxicity may include neuronal cytotoxicity or neuronal cell death". (emphasis added, see page 15, lines 3-13 of the specification). While the specification provides a working example of the method utilizing neuronally differentiated PC12 cells, the specification fails to teach how non-neuronal cells such as glial, microglial, astrocyte, endothelial, and mononuclear cells, can be used in a method for evaluating the ability of a compound to inhibit neurotoxicity as disclosed. There is no teaching in the specification of any correlation between the effects of a compound to inhibit neurotoxicity in cultured non-neuronal cells and the effects of the compound in cultured neuronal cells. In view of applicants' definition of neurotoxicity, and in view of the lack of teaching with regard to the relevance of treating a non-neuronal cell with a compound and the ability of that compound to inhibit neurotoxicity, one of ordinary skill in the art would not know how to make and use the invention as claimed with a high expectation of success and without undue experimentation. Thus, the scope of the claimed invention is not commensurate in scope with the teachings in the specification.

With regard to providing a compound which is a peptidomimetic, the specification does not define what would encompass a suitable peptidomimetic, nor does the specification identify

any particular peptidomimetic or method for selecting a peptidomimetic which is suitable for use in the method for evaluating neurotoxicity. Absent any guidance in the specification for selecting peptidomimetics, one of ordinary skill in the art would not have a high expectation of successfully isolating and utilizing a peptidomimetic in the claimed method without undue experimentation.

With regard to utilizing a compound bound to a solid support, the specification does not define what is intended by a solid support nor does the specification disclose any solid supports which are suitable for use in the claimed method. In addition, the specification does not teach the structures or classes of compounds which may be bound to solid supports. As the specification does not disclose solid supports or compounds which are suitable for attachment to a solid support, one of ordinary skill in the art would not know which supports to use for which compounds, nor would one of ordinary skill in the art know if any and all compounds are actually capable of binding to solid supports. Thus, one of ordinary skill in the art would not have had a high expectation of successfully ascertaining which particular compound should be bound to a particular solid support without undue experimentation.

Claims 11 and 12 are directed to a pharmaceutical composition, wherein the composition comprises a compound which inhibits neurotoxicity and a pharmaceutically acceptable carrier. As written, the pharmaceutical composition encompasses both *in vitro* and *in vivo* applications. Moreover, the compound can encompass macromolecules such as nucleic acids.

While the specification is enabling for providing a pharmaceutical composition to neuronal cells *in vitro* to establish whether the compound inhibits neurotoxicity, the specification is non-enabling for administering a pharmaceutical composition which inhibits neurotoxicity *in vivo*. The specification does not provide any correlation with respect to the *in vitro* and *in vivo* effectiveness of a compound as the inhibition of neurotoxicity has only been demonstrated *in vitro*.

The specification broadly discloses neuronal disorders which can be treated by a compound identified by the claim-designated *in vitro* diagnostic method. The specification only discloses prophetic examples of administering such a composition to treat humans or animals

suffering from neurodegenerative conditions which may be associated with Alzheimer's disease, diabetes, senility, renal failure, hyperlipidemic atherosclerosis, neuronal toxicity, Down's syndrome, dementia associated with head trauma, amyotrophic lateral sclerosis, myasthenia gravis, multiple sclerosis, neuronal degeneration, spongiform encephalopathic diseases, etc. (see page 10, lines 10-34 of the specification). However, the specification does not disclose which compound would be suitable for treating a particular disease, whether the same compound would successfully treat all recited diseases, what dosages and routes of administration of the compound would be effective in treating a specific disclosed disease, and how one would ascertain whether the pharmaceutical composition was effective in ameliorating a specific disclosed disease.

It should also be noted that the state of the art at the time of filing indicates that treating neurodegenerative diseases is neither routine nor predictable. For example, Sabate *et al.* (Clinical Neuroscience, 3:317-321, 1996) indicate that while neurotrophic factors have been shown to promote the survival of particular neuronal populations, the use of classical pharmacotherapy for neurological diseases is restricted by constraints specific to the nervous system. In particular, the blood-brain barrier prevents access to the brain of numerous macromolecules of therapeutic value. Delivery of such molecules requires intracerebral or intracerebroventricular injection, and infusion using osmotic pumps when long-term treatments are necessary. Therefore, the combination of infectious risks and constraints of the delivery technique have precluded the generalized use of drugs (see page 317, right column, last paragraph, bridging page 318). With regard to utilizing pharmaceutical compositions comprising nucleic acids, Sabate *et al.* indicate that gene therapy should enable neurologists to overcome the problems raised by pharmacotherapy. However, Sabate *et al.* caution that there are several important issues to be resolved if gene therapy for neurological diseases is to become a reality including (1) extent of transgene expression, (2) stability of transgene expression, (3) targeting of the cells, (4) safety of the procedure, and (5) the vector large-scale production capacity (see page 318, left column, under "Recombinant Adenovirus For Gene Therapy"). From the teachings of Sabate *et al.*, it is apparent that the art

of pharmacotherapy and gene therapy with respect to treating neurodegenerative diseases is neither routine nor predictable.

In view of the lack of guidance in the specification as to which compounds should be included in the pharmaceutical compositions to treat specific neurodegenerative diseases, the modes of administration which would be effective in treating such neurodegenerative diseases, the lack of working examples which show the effectiveness of treating such neurodegenerative diseases, and the unpredictability of successfully treating neurodegenerative diseases with pharmacotherapy and gene therapy, one of ordinary skill in the art would not have had a high expectation of successfully providing a pharmaceutically composition, for *in vivo* use, which is effective in treating the disclosed neurodegenerative disorders without undue experimentation. Thus, while the specification is enabling for a pharmaceutical composition which can be used in *in vitro* applications, the specification is not enabling for a pharmaceutical composition which can be used in *in vivo* applications.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolozin *et al.* (Science, 274:1710-1713, December 6, 1996, newly applied) in light of Brett *et al.* (Amer. J. Pathol., 143:1699-1712, 1993, newly applied).

Wolozin *et al.* disclose that transfecting neuronally differentiated PC12 cells with a mutant presenilin-2 protein causes increased basal apoptosis in nerve growth factor-differentiated PC12 cells (see, e.g., page 1711, middle column, and Figure 1). In addition, Wolozin *et al.*

disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compound, i.e., pertussis toxin or Aβ(1-42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity (see, e.g., page 1711, middle and right columns, page 1712, left column, Figure 3, and Figure 4E). The Aβ(1-42) compound is added to the cells at a concentration of 10 μM and was generated from a 1 mM Aβ(1-42) stock solution (see, e.g., page 1713, Note #21). Thus, Wolozin *et al.* disclose the claimed method and pharmaceutical composition comprising a compound and a pharmaceutical carrier. It is noted that PC12 cells inherently express a receptor for advanced glycation end product protein (see Brett *et al.*, page 1760, left column).

Thus, the method and pharmaceutical composition disclosed by Wolozin *et al.* anticipates the claimed invention.

Claims 11 and 12 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bartus *et al.* (U.S. Patent No. 5,444,042, 1995) for the reasons of record set forth in the office action of 4/13/99 (Paper No. 7), and the reasons below.

The claims are directed to a pharmaceutical composition comprising a compound capable of inhibiting neurotoxicity, claimed in a product-by-process format.

Bartus *et al.* disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone is sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). Bartus *et al.* teach compounds which inhibit neurotoxicity, i.e., calpain inhibitors. The calpain inhibitors effectively block cell death in an *in vitro* model for neuropathology (see column 73, lines 5-24). The compounds can be formulated as pharmaceutical compositions comprising the compound of interest in a pharmaceutically acceptable formulation containing a carrier material (see column 4, lines 48-54 and column 66, lines 36-40).

Thus, the pharmaceutical composition disclosed by Bartus *et al.* anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolozin *et al.* (Science, 274:1710-1713, December 6, 1996, newly applied) taken with Brett *et al.* (Amer. J. Pathol., 143:1699-1712, 1993, newly applied).

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising compounds identified by the method.

Wolozin *et al.* disclose a method of evaluating the ability of a compound to inhibit neurotoxicity utilizing neuronally differentiated PC12 cells which intrinsically express a receptor for advanced glycation end product protein as disclosed by Brett *et al.*, and as discussed in the 35 U.S.C. 102(b) rejection above.

Wolozin *et al.* do not disclose adding a nucleic acid compound to neuronally differentiated PC12 cells expressing a mutant presenilin-2 protein, or all of the claim-designated pharmaceutical carriers.

However, Wolozin *et al.* disclose adding PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells which do not express a mutant presenilin-2 protein. Addition of the antisense nucleic acid results in a decrease in apoptotic activity in the PC12 cells (see, e.g., page 1720, middle and right columns, and Figure 1). Inasmuch as Wolozin *et al.* disclose that PC12 cells that express a mutant presenilin-2 protein have a high apoptotic activity, it would have been obvious to add PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells expressing mutant presenilin-2 to determine if the antisense nucleic acids are effective in decreasing the observed apoptotic activity in PC12 cells expressing mutant presenilin-2 protein.

With regard to pharmaceutical compositions comprising a compound and a pharmaceutically acceptable carrier, although Wolozin *et al.* do not disclose that the nucleic acid compounds, pertussis toxin compound or Aβ(1-42) compound is admixed with all of the claim-designated pharmaceutical carriers, it is well established in the art of cell culture to admix compounds with solutions containing water, buffers, salts, or other suitable carriers prior to adding the compound of interest to the culture. One of ordinary skill in the art would have been motivated to admix the compound of interest with a suitable carrier to more easily control the concentration of the compound added to the cell culture and to avoid a localized high concentration of a solid compound which may be detrimental to the cells.

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to modify the method of Wolozin *et al.* by substituting the peptide compounds added to the mutant presenilin-2 expressing PC12 cells with nucleic acid compounds such as antisense PS-2 or ALG-3 to determine the ability of these compounds to inhibit neurotoxicity. As Wolozin *et al.* was successful in evaluating the effect of these compounds on neurotoxicity in PC12 cells expressing normal presenilin-2, one of ordinary skill in the art would have had a high expectation of successfully evaluating the effect of these compounds on mutant

presenilin-2 expressing PC12 cells without undue experimentation. Moreover, adding the nucleic acids, or other compounds such as pertussis toxin or Aβ(1-42) to cell cultures as a pharmaceutical composition would have been obvious and well within the purview of one of ordinary skill in the art of cell culture for the reasons set forth above.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

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